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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,664	02/18/2004	Felix A. Montero-Julian	2512.021000/KWM(2052-183)	5199
64562	7590	03/02/2009	EXAMINER	
STERNE KESSLER GOLDSTEIN & FOX, P.L.L.C. 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005			DIBRINO, MARIANNE NMN	
		ART UNIT	PAPER NUMBER	
		1644		
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		03/02/2009	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,664	MONTERO-JULIAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12/11/08 & 4/24/08.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-9, 11, 13-16, 20-34, 36, 38-41, 45-50 and 73-84 is/are pending in the application.
- 4a) Of the above claim(s) 7, 8, 15, 16, 23, 24, 32, 33, 39-41, 48, 49 and 78 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-6, 9, 11, 13, 14, 20-22, 25-31, 34, 36, 38, 45-47, 50, 73-77 and 79-84 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/21/08 & 6/26/08</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/24/08 has been entered.

Applicant's amendment filed 12/11/08 and Applicant's responses filed 4/24/08 and 8/1/08 are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election of Group I, and species of HLA-A2/ β 2m/MART-1 as the MHC/template peptide complex in Applicant's responses filed 3/27/07 and 11/13/06. In addition, Applicant is reminded of Applicant's election of the species 100x molar excess of competitor peptide, incubating the sample for about 2-20 hours at about 21 degrees C, HBc 18-27 tagged with FITC as the tracer peptide, only one competitor peptide is used and soluble HLA molecule in Applicant's response filed 3/27/07.

Claims 1-6, 9, 11, 13, 14, 20-22, 25-31, 34, 36, 38, 45-47, 50, 73-77 and 79-84 read on the elected species.

Accordingly, claims 7, 8, 15, 16, 23, 24, 32, 33, 39-41, 48, 49, 78 (non-elected species of Group I) remain withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-6, 9, 11, 13, 14, 20-22, 25-31, 34, 36, 38, 45-47, 50, 73-77 and 79-84 are currently being examined.

3. With regard to Applicant's arguments (at section III on pages 12-13 of the amendment filed 4/24/08) to the finality of the prior Office Action, the following applies. The new grounds of rejection were necessitated by Applicant's amendment of the base claims 1 and 26 to recite "wherein the MHC monomer is HLA-A2", forming a combination of limitations not previously present in the said claims 1 and 26, and by Applicant's submission of the IDS reference WO 92/07952 A1 filed 7/12/07. The '286, '632 and '262 publications argued by Applicant to be newly cited references, are secondary references that in combination with the said IDS references form the basis for rejections under 35 USC 103(a) of record in the prior Office Action.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 recites the limitation "system" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Base claim 73 recites "kit".

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 (of record).

WO 92/07952 A1 teaches determining the binding affinity of a candidate peptide for a specific MHC molecule (*i.e.*, MHC heavy chain and β 2m) using competition between detectable agonist peptide (a peptide known to bind to MHC that may or may not be labeled with fluorophore (claims 6 and 31) such as fluorescein (FITC) (claims 9 and 34)) and the candidate peptide (*i.e.*, a peptide that is a competitor peptide) in up to 100-fold more from the agonist peptide. WO 92/07952 A1 teaches testing one or more concentration of candidate peptide on binding of the agonist peptide. WO 92/07952 A1 teaches an incubation time between about 12 and 48 hours at, for example, 37 degrees C (*i.e.*, "about 21 degrees C) (pages 8-9 at line 32, paragraph spanning pages 7-8). WO 92/07952 A1 teaches preloading an isolated MHC glycoprotein with a homogeneous peptide preparation, the peptide chosen to be comparatively readily released by the MHC molecule (especially page 13 at lines 19-35, page 14 at lines 1-23, page 4 at the last paragraph, and claims). WO 92/07952 A1 teaches separating the bound agonist from the unbound agonist and detecting the amount of agonist bound in the complex as a function of the concentration of test compound in the reaction mixture, including coupling the agonist peptide to biotin and separating by means of coupling the complex to a solid support via linkage with streptavidin (see entire reference, especially claims).

WO 92/07952 A1 does not teach that the MHC molecule is HLA-A2.

US 2003/0191286 A1 discloses making soluble MHC class I molecules, including HLA-A2, with or without endogenous peptides loaded therein, and further discloses representative HLA-A2 binding peptides of nine or ten amino acid residues in length (see entire reference, especially [0157], [0032], [0190] and claims). US 2003/0191286 A1 further discloses at [0085] "Cloned genomic DNA fragments contain both exons and introns as well as other non-translated regions at the 5' and 3' termini of the gene. Following transfection into a cell line which transcribes the genomic DNA (gDNA) into RNA, cloned genomic DNA results in a protein product thereby removing introns and splicing the RNA to form messenger RNA (mRNA), which is then translated into an MHC protein. Transfection of MHC molecules encoded by gDNA therefore facilitates re-isolation of the gDNA, mRNA/cDNA, and protein. Production of MHC molecules in non-mammalian cell lines such as insect and bacterial cells requires cDNA clones, as these lower cell types do not have the ability to splice introns out of RNA transcribed from a gDNA clone. In these instances the mammalian gDNA transfectants of the present invention provide a valuable source of RNA which can be reverse transcribed to form MHC cDNA. The cDNA can then be cloned, transferred into cells, and then translated into protein. In addition to producing secreted MHC, such gDNA transfectants therefore provide a ready source of mRNA, and therefore cDNA clones, which can then be transfected into non-mammalian cells for production of MHC. Thus, the present invention which starts with MHC genomic DNA clones allows for the production of MHC in cells from various species."

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the soluble HLA-A2 monomers disclosed by US 2003/0191286 A1 as the MHC molecule in the method taught by WO 92/07952 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 92/07952 A1 teaches a method of determining binding affinity of a candidate peptide for a specific MHC molecule, and US 2003/0191286 A1 discloses that HLA-A2 is a specific MHC molecule and further discloses methods to make soluble MHC molecules.

Although the art reference does not explicitly teach "wherein the template peptide has lower or intermediate affinity as compared with the tracer peptide for the monomer," the art reference teaches there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the limitation recited in instant claims 4 and 29 “wherein said liquid phase condition includes incubating the sample for about 2 to 20 hours,” the art reference teaches incubating 2 days or 48 hours, and so meets the claim limitation.

With regard to the limitation recited in instant claims 5 and 30, “wherein said liquid phase condition further includes incubating the sample at about 21 degrees C,” the art reference teaches incubating at room temperature of 37 degrees C, and so meets the claim limitation.

Claims 1-6, 9, 11, 20-22 and 25 are included in this rejection because the art method of measuring affinity of a peptide of interest is also identifying said peptide for binding to MHC.

With regard to the recited limitation in instant claims 3 and 28, the said limitation is not a test step. Although the art reference does not explicitly teach “wherein the tracer peptide displaces at least 90% of the template peptide in a parallel competition assay conducted in the absence of the first competitor peptide,” the art reference teaches there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant’s arguments have been fully considered, but are not persuasive.

Applicant’s said arguments are of record on pages 14-17 and on pages 19-21. Briefly, Applicant asserts that the cited art references fail to teach or suggest the claimed methods, provide no apparent reason to combine the references and a person of ordinary skill in the art would have no reasonable expectation of success in making the claimed invention.

Applicant further argues that the amended claims now require that the HLA-A2 monomer is recombinantly produced in an expression system selected from the group consisting of a prokaryotic, yeast, plant and insect expression system. Applicant argues that Rothbard (*i.e.*, WO 92/07952 A1) discloses assays using MHC class II glycoproteins and thus fails to teach the HLA-A2 monomer, while Hildebrand (*i.e.*, US 2003/0191286 A1) discloses recombinant class I glycoprotein produced only in mammalian cell lines, but not in prokaryotic, yeast, plant or insect expression systems, thus provides no disclosure of the specific HLA-A2 monomer used in Applicant’s claimed method.

However WO 92/07952 A1 does teach assays using MHC glycoproteins, either class I and class II, while exemplifying class II (especially abstract, claims and pages 1-6). In addition, Applicant is arguing WO 92/07952 A1 separately. In contrast to Applicant's assertion, US 2003/0191286 A1 discloses producing HLA class I in insect cells or in bacterial cells (*i.e.*, prokaryotic cells). Furthermore, the limitation in base claims 1 and 26, *i.e.*, "wherein said monomer is produced in an expression system selected from the group consisting of a prokaryotic system, a yeast system, a plant system and an insect system" is not a method step. Absent a structural difference between the claimed HLA-A2 molecule and the art HLA-A2 molecule, the "wherein" clause does not distinguish the said HLA-A2 molecule from the art molecule.

Applicant further asserts that the MHC Class II molecules taught by the primary reference are structurally different than the MHC class I molecules taught by the secondary reference, and that it was well known that different approaches are necessary for MHC class I and class II molecules. Applicant cites Exhibit C at page 6 that notes that structural differences between class I and class II molecules necessitate different approaches to tetramer design and use, notably that it was known that an MHC class II molecule cannot be renatured to form a ternary structure while MHC class I can be efficiently renatured in the presence of antigenic peptides to yield a ternary complex. Applicant concludes therefrom, a person of ordinary skill in the art would not have thought that the MHC class I molecule in the secondary reference can replace the MHC class II molecule used in the assay taught by the primary reference that uses class II MHC.

However, Applicant's latter argument would support that there would be a reasonable expectation of success in use of class I MHC, as WO 92/07952 A1 does teach assays using MHC glycoproteins, either class I and class II, while exemplifying class II (especially abstract, claims and pages 1-6). Applicant's argument directed at Exhibit C is a mischaracterization. While it was known that MHC class I and class II molecules have different structures, page 6 at Exhibit C discusses the difference between single-chain class I molecules and non-single chain class II molecules that are non-covalent $\alpha\beta$ dimers, and also discusses producing class II molecules as single chain molecules with peptide or producing exogenous peptide loaded biotinylated class II $\alpha\beta$ dimers, followed by multimerization with avidin in order to circumvent the problems of detecting the low frequency of antigen specific T cells in human peripheral blood and the low avidity of binding between the TCR and the MHC/peptide complex. Exhibit C at page 6 does not say that MHC class II cannot be renatured to form a ternary structure with peptide, just that the dimers of class II $\alpha\beta$ chains have a variable range of stability and solubility in solution. The cited teaching is not relevant to the instant rejection, particularly since the primary reference exemplifies use of soluble MHC class II in solution in the complex formation with peptide, and the primary reference also clearly envisions use of MHC class I molecules in the assay taught by the primary reference. If

various MHC class II molecules have different ranges of stability and solubility in solution, this is not a teaching that class I molecules may not be used in the assay.

Applicant offers as an argument for there being no reasonable expectation of success in combining the references, that it was well known in the art that class I cannot simply replace class II due to its structural differences as evidenced in Exhibit C. Furthermore, the MHC class I produced in mammalian cells similar to US 2003/0191286 A1 cannot be used in a sensitive assay system such as taught by US 2003/0191286 A1, and Applicant offers paragraph [0084] of US 2003/0191286 A1 as evidence. Applicant asserts that unlike US 2003/0191286 A1, prokaryotic cells transformed with a vector encoding an HLA-A2 monomer may not express any endogenous MHC glycoprotein because the prokaryotic cells lack endogenous genes encoding the MHC molecules and this property effectively eliminates the cumbersome steps of removing endogenously expressed MHC glycoprotein from the recombinantly produced MHC monomer. Applicant concludes that in view of the problems readily apprehended from the cited references, a person of ordinary skill in the art would not have had any reasonable expectation of success in making or using the claimed invention.

However, the arguments with regard to Exhibit C and structural differences between class I and class II have been address supra. In addition, no teaching exists in the art references to support Applicant's assertion that MHC class I produced in mammalian cells similar to US 2003/0191286 A1 cannot be used in a sensitive assay system such as taught by US 2003/0191286 A1. The issue of using prokaryotic cells is only relevant to that fact that they do not contain genes for endogenous MHC. In light of the secondary references teaching use of prokaryotic and insect cells, Applicant's argument is off point.

Applicant also asserts that the Examiner used hindsight in combining the references of the instant rejection and that it is not permissible to pick and choose among isolated disclosure in the references.

However, Applicant appears to be picking and choosing among the reference teachings, ignoring for instance, the teaching of use of prokaryotic and insect cells to produce recombinant soluble MHC class I molecules.

One of ordinary skill in the art would have been motivated to make the claimed invention given the teachings of the combined references, and with a reasonable expectation of success, in order to perform the assay taught in the primary reference with an MHC class I molecule as taught by the primary reference, using an MHC class I molecule from humans, HLA-A2, that is disclosed by the secondary reference, for the reasons of record and those enunciated herein supra.

8. The prior rejection of record of claims 17 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 as applied to claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 above [now claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47 and 50], and further in view of US 20040253632 A1 has been withdrawn in view of Applicant's cancellation of claims 17 and 42.

9. The prior rejection of record of claims 13 and 38 under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 as applied to claims 1-9, 11, 20-22, 25-34, 36, 45-47 and 50 above [now claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47 and 50], and further in view of US 20040072262 A1 has been withdrawn in view of Applicant's statement "Because the reference [US 20040072262 A1] was owned at the time of the invention of the present application by Beckman Coulter, Inc., or subject to the assignment to Beckman Coulter, Inc., 35 U.S.C. 103(c) provides that the reference may not be applied against the present application." (Applicant's said statement is of record in the amendment filed 4/24/08 on pages 17-19).

10. Claims 13, 14, 38, 73-77, 80, 82, 83 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 (of record) as applied to claims 1-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 above, and further in view of Mitchell *et al* (Cancer Research 2000, 60: 6448-6456), US 2004/0214995A1 and US 2002/0106708 A1 (IDS reference filed 6/26/08).

The combination of WO 92/07952 A1 and US 2003/0191286 A1 has been discussed above, hereafter referred to as "the combined references."

The combined references do not teach wherein the monomer is HLA-A2/MART-1₂₆₋₃₅ (claims 13 and 38), nor wherein the tracer peptide is HBc 18-27 (claim 14), nor wherein the HLA-A2 monomer is that produced in *E. coli* (claims 80, 82 and 84), nor wherein the ternary complex comprising the HLA-A2 monomer with template MHC-binding peptide and the tracer peptide tagged with a detectable label are comprised in a kit for identifying an MHC binding peptide for the HLA-A2 monomer (claims 73-77, 83 and 84), nor wherein the kit further comprises an instruction for using the kit (claim 74).

Mitchell *et al* teaches use of the HBc 18-27 peptide labeled with a detectable label and competing unlabeled putative epitope peptides for binding to HLA-A2.

US 2004/0214995A1 discloses the low affinity peptide MART-1₂₆₋₃₅ that binds to HLA-A2 ([0224]), and also discloses the production of proteins in *E. coli*. US 2002/0106708 A1 discloses placing components of assays into kits (see entire reference).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the MART-1₂₆₋₃₅ peptide as the template MHC binding peptide bound to HLA-A2 in the method taught by the combined references, to have used an HLA-A2 monomer that was produced in *E. coli*, and to have placed the components of the assay (*i.e.*, the monomer with template binding peptide bound thereto and a tracer MHC-binding peptide tagged with a detectable label) in a kit, including with instructions for use.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 92/07952 A1 of the combined references teaches preloading an isolated MHC glycoprotein with a homogeneous peptide preparation, the peptide chosen to be comparatively readily released by the MHC molecule, and US 2004/0214995A1 discloses that the peptide MART-1₂₆₋₃₅ exhibits low affinity binding to HLA-A2, while Mitchell *et al* teaches use of the HBC 18-27 peptide labeled with a detectable label as a tracer peptide. One of ordinary skill in the art at the time the invention was made would have been motivated to have used HLA-A2 that was produced in *E. coli* because US 2003/0191286 A1 discloses making HLA-A2 in bacterial cells and US 2004/0214995A1 discloses that recombinant proteins may be produced in *E. coli*. One of ordinary skill in the art at the time the invention was made would have been motivated to have placed the components of the assay in a kit for convenience sake.

11. No claim is allowed.
12. With regard to Applicant's Form 1449 filed 6/26/08: The reference listed as "FP1" has been crossed out by the Examiner because it is a duplicate citation of one in the Form 1449 filed on 7/12/07. In addition, reference "NPL28" has been crossed out because it is not a complete citation.
13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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February 23, 2009

/G.R. Ewoldt/
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